

## X-ray Structures of the *Escherichia coli* Periplasmic Binding Protein FhuD Complexed to Ferric Siderophores

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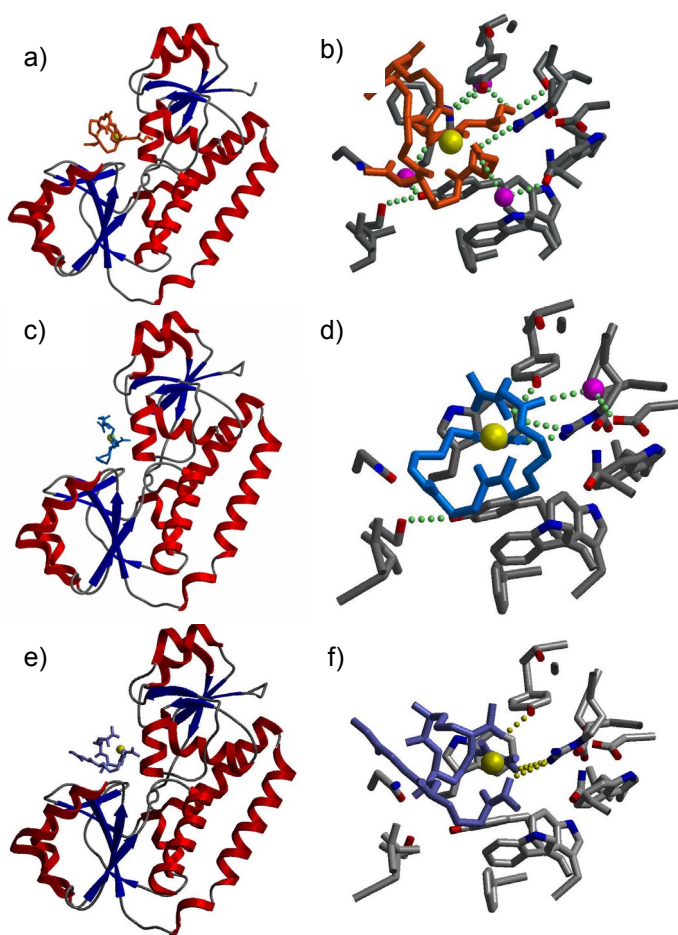
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**Introduction:** Siderophore-binding proteins play an essential role in the uptake of iron in many gram-positive and gram-negative bacteria. FhuD is an ATP-binding cassette-type (ABC-type) binding protein involved in the uptake of hydroxamate-type siderophores and is considered to be a potential drug target. The crystal structure of FhuD from *Escherichia coli* complexed with the ferrichrome homolog gallichrome has been determined at 1.9 Å resolution, representing the first structure of an ABC-type binding protein involved in the uptake of siderophores. The gallichrome binds in a shallow hydrophobic pocket between the two domains of the protein. Crystal structures of FhuD complexed with other siderophores, such as coprogen, Desferal, and the antibiotic albomycin show that binding occurs in a similar manner, with slight movement of amino acid side chains within the binding pocket. Unlike most periplasmic ligand binding proteins (PLBPs), the two domains of FhuD are connected by a long  $\alpha$ -helix. This rigid architecture may lack the ability to undergo the large conformational changes typically observed in PLBPs upon ligand binding. This study provides a basis for the rational design of novel bacteriostatic agents, including siderophore-antibiotic conjugates that can act as "Trojan horses", using the ferrichrome uptake system to deliver antibiotics directly into targeted pathogens.

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**References:** T.E. Clarke, S.-Y. Ku, D. Dougan, H.J. Vogel, and L.W. Tari, "X-ray Structures of the *Escherichia coli* Periplasmic Binding Protein FhuD complexed to Ferric Siderophores," The 14<sup>th</sup> Symposium of the Protein Society, San Diego, CA, 2000.



**Figure 1.** Comparison of FhuD bound to various siderophores. a) FhuD bound to the fungal siderophore coprogen, with a close-up view of the binding site in b). c) FhuD bound to the drug Desferal, with a detailed view of binding in d). In e) and f) FhuD bound with the antibiotic albomycin. The overall structure of the protein remains similar, but small changes in the position of the amino acid side chains accommodate different ligands.